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(FILE 'HOME' ENTERED AT 13:48:37 ON 26 OCT 2005)

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FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 13:49:06 ON 26 OCT 2005

L1	13	SEA ABB=ON PLU=ON	(PIPKI OR PIPK) (3A) 661
L2	458	SEA ABB=ON PLU=ON	PHOSPHATIDYLINOSITOL PHOSPHATE (2W) KINASE
L3	16	SEA ABB=ON PLU=ON	L2 AND 661
L4	16	SEA ABB=ON PLU=ON	L1 OR L3
L5	133994	SEA ABB=ON PLU=ON	CELL (3A) MIGRAT?
L6	7	SEA ABB=ON PLU=ON	L4 AND L5
L7	24	SEA ABB=ON PLU=ON	L2 AND L5
L8	14	SEA ABB=ON PLU=ON	L7 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L9	14	SEA ABB=ON PLU=ON	L6 OR L8
L10	9	DUP REM L9 (5 DUPLICATES REMOVED)	
		ANSWERS '1-5' FROM FILE CAPLUS	
		ANSWERS '6-7' FROM FILE EMBASE	
		ANSWERS '8-9' FROM FILE BIOSIS	
		D SCAN TI	
L11	37	SEA ABB=ON PLU=ON	(PIPKI OR PIPK) (3A) GAMMA
L12	23	SEA ABB=ON PLU=ON	L11 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L13	18	SEA ABB=ON PLU=ON	L12 NOT L10
L14	16	DUP REM L13 L10 (11 DUPLICATES REMOVED)	
		ANSWERS '1-8' FROM FILE CAPLUS	
		ANSWER '9' FROM FILE MEDLINE	
		ANSWER '10' FROM FILE EMBASE	
		ANSWERS '11-16' FROM FILE BIOSIS	
L15	25867	SEA ABB=ON PLU=ON	ANDERSON R?/AU
L16	950	SEA ABB=ON PLU=ON	LING K?/AU
L17	21	SEA ABB=ON PLU=ON	DOUGHMAN R?/AU
L18	26801	SEA ABB=ON PLU=ON	(L15 OR L16 OR L17)
L19	74	SEA ABB=ON PLU=ON	L18 AND (L1 OR L2 OR L11)
L20	14	SEA ABB=ON PLU=ON	L19 AND (L1 OR L11)
L21	74	SEA ABB=ON PLU=ON	L18 AND L2
L22	26	SEA ABB=ON PLU=ON	L21 AND (SRC OR FAK OR MODULAT? OR ADHES?)
L23	26	SEA ABB=ON PLU=ON	L20 OR L22
L24	13	DUP REM L23 (13 DUPLICATES REMOVED)	
		ANSWERS '1-8' FROM FILE CAPLUS	
		ANSWERS '9-13' FROM FILE BIOSIS	
L25	3	SEA ABB=ON PLU=ON	L24 NOT L14

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=> fil caplus medline embase biosis
FILE 'CAPLUS' ENTERED AT 13:53:59 ON 26 OCT 2005
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=> d que l14
L1            13 SEA (PIPKI OR PIPK) (3A) 661
L2           458 SEA PHOSPHATIDYLINOSITOL PHOSPHATE (2W) KINASE
L3            16 SEA L2 AND 661
L4            16 SEA L1 OR L3
L5        133994 SEA CELL (3A) MIGRAT?
L6             7 SEA L4 AND L5
L7            24 SEA L2 AND L5
L8            14 SEA L7 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L9            14 SEA L6 OR L8
L10            9 DUP REM L9 (5 DUPLICATES REMOVED)
L11           37 SEA (PIPKI OR PIPK) (3A) GAMMA
L12           23 SEA L11 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L13           18 SEA L12 NOT L10
L14           16 DUP REM L13 L10 (11 DUPLICATES REMOVED)


=> d

L14  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2005 ACS on STN DUPLICATE 1
AN   2005:536221  CAPLUS
DN   143:188973
TI   Phosphatidylinositol Phosphate Kinase Type Iγ Directly Associates
     with and Regulates Shp-1 Tyrosine Phosphatase
AU   Bairstow, Shawn F.; Ling, Kun; Anderson, Richard A.
CS   Department of Pharmacology, University of Wisconsin Medical School,
     Madison, WI, 53706, USA
SO   Journal of Biological Chemistry (2005), 280(25), 23884-23891
     CODEN: JBCHA3; ISSN: 0021-9258
PB   American Society for Biochemistry and Molecular Biology
DT   Journal
LA   English
RE.CNT  36    THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d .ca l14 1-8;d ibib ab ct l14 9-16

L14  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:536221  CAPLUS
DOCUMENT NUMBER:          143:188973
TITLE:                    Phosphatidylinositol Phosphate Kinase Type Iγ
                          Directly Associates with and Regulates Shp-1 Tyrosine
                          Phosphatase
AUTHOR(S):                Bairstow, Shawn F.; Ling, Kun; Anderson, Richard A.
```

CORPORATE SOURCE: Department of Pharmacology, University of Wisconsin Medical School, Madison, WI, 53706, USA
SOURCE: Journal of Biological Chemistry (2005), 280(25), 23884-23891
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Jun 2005

AB Tyrosine phosphorylation plays a critical role in many regulatory aspects of cellular signaling, and dephosphorylation of phosphotyrosine residues is crucial for termination of signals initiated by tyrosine kinases. Previous work has shown that the tyrosine kinase **Src** phosphorylates Tyr644 on phosphatidylinositol phosphate kinase type I (**PIPKI**) γ 661 in a focal **adhesion** kinase-dependent manner. Phosphorylation of this residue is essential for high affinity binding of **PIPKI**γ 661 to the focal **adhesion** protein talin and for targeting of **PIPKI. gamma.**661 to focal **adhesions.** A yeast two-hybrid screen performed with the C-terminal 178-amino acid tail of **PIPKI. gamma.**661 identified an interaction with the phosphatase domain of the tyrosine phosphatase Shp-1. The interaction between **PIPKI. gamma.**661 and Shp-1 was confirmed via co-immunopptn. from HEK293 cell lysates. In addition, **Src**-phosphorylated **PIPKI. gamma.**661 is a substrate for Shp-1, and Shp-1 **modulates** both the association between **PIPKI**γ 661 and talin and the targeting of **PIPKI**γ 661 to focal **adhesions** in mammalian cells. Finally, the authors showed that Shp-1 phosphatase activity is inhibited by the product of **PIPKI. gamma.**661, phosphatidylinositol 4,5-bisphosphate, in vitro. These combined results suggest a model in which the reciprocal actions of **Src** tyrosine kinase and Shp-1 tyrosine phosphatase dynamically regulate the association between **PIPKI**γ 661 and talin.

CC 7-3 (Enzymes)
Section cross-reference(s): 13

IT Cell junction
(focal contact; phosphatidylinositol phosphate kinase type Iγ binding and regulation of tyrosine phosphatase Shp-1 in relation to **FAK** kinase-dependent talin binding and kinase targeting to focal **adhesions**)

IT Human
Molecular association
(phosphatidylinositol phosphate kinase type Iγ binding and regulation of tyrosine phosphatase Shp-1 in relation to **FAK** kinase-dependent talin binding and kinase targeting to focal **adhesions**)

IT Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phosphatidylinositol phosphate kinase type Iγ binding and regulation of tyrosine phosphatase Shp-1 in relation to **FAK** kinase-dependent talin binding and kinase targeting to focal **adhesions**)

IT 59977-48-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Iγ; phosphatidylinositol phosphate kinase type Iγ binding and regulation of tyrosine phosphatase Shp-1 in relation to **FAK** kinase-dependent talin binding and kinase targeting to focal **adhesions**)

IT 300855-77-0, Protein tyrosine phosphatase Shp-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phosphatidylinositol phosphate kinase type Iγ binding and regulation of tyrosine phosphatase Shp-1 in relation to **FAK** kinase-dependent talin binding and kinase targeting to focal **adhesions**)
IT 144114-16-9, Focal **adhesion** kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tyrosine phosphatase Shp-1 inhibition by phosphatidylinositol bisphosphate in relation to phosphatidylinositol phosphate kinase Iγ)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:168211 CAPLUS
DOCUMENT NUMBER: 142:406442
TITLE: Structural Basis for Phosphatidylinositol Phosphate Kinase Type Iγ Binding to Talin at Focal **Adhesions**
AUTHOR(S): de Pereda, Jose M.; Wegener, Kate L.; Santelli, Eugenio; Bate, Neil; Ginsberg, Mark H.; Critchley, David R.; Campbell, Iain D.; Liddington, Robert C.
CORPORATE SOURCE: Program on Cell Adhesion, Burnham Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Biological Chemistry (2005), 280(9), 8381-8386
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 28 Feb 2005
AB The cytoskeletal protein talin binds to a short C-terminal sequence in phosphatidylinositol phosphate kinase type Iγ (**PIPKIγ**), activating the enzyme and promoting the local production of phosphatidylinositol 4,5 bisphosphate, which regulates focal **adhesion** dynamics as well as clathrin-mediated endocytosis in neuronal cells. Here we show by crystallog., NMR, and calorimetric anal. that the phosphotyrosine binding (PTB)-like domain of talin engages the **PIPKIγ** C terminus in a mode very similar to that of integrin binding. However, **PIPKIγ** binds in the canonical PTB-peptide mode with an SPLH motif replacing the classic NPXY motif. The tighter packing of the SPLH motif against the hydrophobic core of talin may explain the stronger binding of **PIPKI. gamma.**. Two tyrosine residues flanking the SPLH motif (Tyr-644 and Tyr-649) have been implicated in the regulation of talin binding. We show that phosphorylation at Tyr-644, a **Src** phosphorylation site in vivo, has little effect on the binding mode or strength, which is consistent with modeling studies in which the phosphotyrosine makes surface-exposed salt bridges, and we suggest that its strong activating effect arises from the release of autoinhibitory restraints in the full-length **PIPKIγ** . Modeling studies suggest that phosphorylation of Tyr-649 will likewise have little effect on talin binding, whereas phosphorylation of the SPLH serine is predicted to be strongly disruptive. Our data are consistent with the proposal that **Src** activity promotes a switch from integrin binding to **PIPKIγ** binding that regulates focal **adhesion** turnover.
CC 7-3 (Enzymes)

Section cross-reference(s): 13, 75
ST crystal structure phosphatidylinositol phosphate kinase Igamma talin focal **adhesion**
IT Talin
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(FERM F3 domain of, fusion with a phosphatidylinositol phosphate kinase Iγ fragment; structural basis for phosphatidylinositol phosphate kinase type Iγ binding to talin at focal **adhesions**)
IT Cell junction
(focal contact; structural basis for phosphatidylinositol phosphate kinase type Iγ binding to talin at focal **adhesions**)
IT Phosphorylation, biological
(protein; **Src** activity promotes a switch from integrin binding to **PIPKI**γ binding that regulates focal **adhesion** turnover)
IT Conformation
(protein; structural basis for phosphatidylinositol phosphate kinase type Iγ binding to talin at focal **adhesions**)
IT Molecular association
Molecular recognition
(structural basis for phosphatidylinositol phosphate kinase type Iγ binding to talin at focal **adhesions**)
IT 141349-89-5, **Src** tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Src** activity promotes a switch from integrin binding to **PIPKI**γ binding that regulates focal **adhesion** turnover)
IT 59977-48-9D, Iγ, fragment of, fusion with talin FERM F3 domain
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structural basis for phosphatidylinositol phosphate kinase type Iγ binding to talin at focal **adhesions**)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2005:207606 CAPLUS
DOCUMENT NUMBER: 142:237160
TITLE: Regulation of the interaction between PIPKIγ and talin by proline-directed protein kinases
AUTHOR(S): Lee, Sang Yoon; Voronov, Sergey; Letinic, Kresimir; Nairn, Angus C.; Di Paolo, Gilbert; De Camilli, Pietro
CORPORATE SOURCE: Howard Hughes Medical Institute and Department of Cell Biology, Yale University School of Medicine, New Haven, CT, 06510, USA
SOURCE: Journal of Cell Biology (2005), 168(5), 789-799
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 09 Mar 2005
AB The interaction of talin with phosphatidylinositol(4) phosphate 5 kinase type Iγ (PIPKIγ) regulates PI(4,5)P2 synthesis at synapses and at focal **adhesions**. Here, we show that phosphorylation of serine 650 (S650) within the talin-binding sequence of human PIPKIγ blocks this interaction. At synapses, S650 is phosphorylated by p35/Cdk5 and mitogen-activated protein kinase at rest, and dephosphorylated by calcineurin upon stimulation. S650 is also a substrate for cyclin B1/Cdk1 and its phosphorylation in mitosis correlates with focal **adhesion**

disassembly. Phosphorylation by **Src** of the tyrosine adjacent to S650 (Y649 in human PIPKIγ) was shown to enhance PIPKIγ targeting to focal **adhesions.** We find that Y649 phosphorylation does not stimulate directly PIPKIγ binding to talin, but may do so indirectly by inhibiting S650 phosphorylation. Conversely, S650 phosphorylation inhibits Y649 phosphorylation by **Src.** The opposite effects of the phosphorylation of Y649 and S650 likely play a critical role in regulating synaptic function as well as the balance between cell **adhesion** and cell motility.

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 6

ST **phosphatidylinositol phosphate kinase** serine phosphorylation Cdk5 talin assocn synapse; PIPKIgamma tyrosine phosphorylation **src** kinase focal **adhesion** fibroblast; ERK1 ERK2 kinase calcineurin PIPKIgamma dephosphorylation **cell adhesion migration**; cyclin B1 Cdk1 kinase PIPKIgamma phosphorylation mitosis

IT Molecular association
(PIPKIγ - talin; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Dephosphorylation, biological
(PIPKIγ, by calcineurin; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Cell junction
(focal contact, PIPKIγ targeting to; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Biological transport
(intracellular, PIPKIγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Protein motifs
(phosphorylation site, Ser-650 in talin-binding sequence of PIPKIγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Protein motifs
(phosphorylation site, Y649 in PIPKIγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Phosphorylation, biological
(protein, PIPKIγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT **Adhesion**, biological
Cell migration
Fibroblast
Human
Mitosis
Synapse
(regulation of interaction between human PIPKIγ and talin by

PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study) (regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT Organelle
(stress fiber; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT 361540-77-4, Calcineurin
RL: BSU (Biological study, unclassified); BIOL (Biological study) (PIPKIγ dephosphorylation by; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT 137632-07-6, ERK1 kinase 137632-08-7, ERK2 kinase 146702-82-1, Cyclin B1-Cdc2 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (PIPKIγ phosphorylation by; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT 56-45-1, L-Serine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Ser-650, Cdk5 phosphorylation site in PIPKIγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT 60-18-4, L-Tyrosine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Y649, **Src** phosphorylation site in PIPKIγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT 144697-17-6, Gene c-**src** kinase 147014-96-8, CDK5 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

IT 104645-76-3, Phosphatidylinositol(4) phosphate 5 kinase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(type Iγ; regulation of interaction between human PIPKIγ and talin by PIPKIγ phosphorylation induced by proline-directed protein kinases in synapses in relation to cell cycle, **adhesion**, and motility)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2004:1715 CAPLUS
DOCUMENT NUMBER: 140:124315
TITLE: Tyrosine phosphorylation of type Iγ **phosphatidylinositol phosphate**

kinase by **Src** regulates an integrin-talin switch

AUTHOR(S): Ling, Kun; Doughman, Renee L.; Iyer, Vidhya V.; Firestone, Ari J.; Bairstow, Shawn F.; Mosher, Deane F.; Schaller, Michael D.; Anderson, Richard A.

CORPORATE SOURCE: Department of Pharmacology, Program in Molecular and Cellular Pharmacology, University of Wisconsin Medical School, Madison, WI, 53706, USA

SOURCE: Journal of Cell Biology (2003), 163(6), 1339-1349
CODEN: JCLBA3; ISSN: 0021-9525

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 02 Jan 2004

AB Engagement of integrin receptors with the extracellular matrix induces the formation of focal **adhesions** (FAs). Dynamic regulation of FAs is necessary for **cells** to polarize and **migrate.** Key interactions between FA scaffolding and signaling proteins are dependent on tyrosine phosphorylation. However, the precise role of tyrosine phosphorylation in FA development and maturation is poorly defined. Here, we show that phosphorylation of type Iγ **phosphatidylinositol phosphate kinase** (**PIPKI**.gamma.**661**) on Tyr644 residue is critical for its interaction with talin, and consequently, localization to FAs. **PIPKI**.gamma.**661** is specifically phosphorylated on Y644 by **Src.** Phosphorylation is regulated by focal **adhesion** kinase, which enhances the association between **PIPKI**.gamma.**661** and **Src.** The phosphorylation of Y644 results in an .apprx.15-fold increase in binding affinity to the talin head domain and blocks β-integrin binding to talin. This defines a novel phosphotyrosine-binding site on the talin F3 domain and a "mol. switch" for talin binding between **PIPKI** .gamma.**661** and β-integrin that may regulate dynamic FA turnover.

CC 6-3 (General Biochemistry)
Section cross-reference(s): 7

ST tyrosine phosphorylation **phosphatidylinositol phosphate kinase src** integrin talin

IT Signal transduction, biological
(Tyr644 residue phosphorylation of type Iγ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)

IT Integrins
Phosphatidylinositol 4,5-bisphosphate
Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Tyr644 residue phosphorylation of type Iγ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)

IT Cell junction
(focal contact; Tyr644 phosphorylation regulates **phosphatidylinositol phosphate kinase**-talin association and focal contact targeting of **phosphatidylinositol phosphate kinase**)

IT Phosphorylation, biological
(protein; Tyr644 residue phosphorylation of type Iγ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)

IT Protein motifs
(talin head domain; Tyr644 residue phosphorylation of type Iγ **phosphatidylinositol phosphate kinase** by

Src kinase regulates integrin-talin switch)
IT 56-87-1, L-Lysine, biological studies 74-79-3, L-Arginine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Lys357 and Arg358 residues of talin promote its binding to phosphorylated **phosphatidylinositol phosphate kinase**)
IT 60-18-4, L-Tyrosine, biological studies 59977-48-9 141349-89-5, Gene **src** kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Tyr644 residue phosphorylation of type Iγ **phosphatidylinositol phosphate kinase** by **Src** kinase regulates integrin-talin switch)
IT 80449-02-1, Nonreceptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (c-**Src** association with **phosphatidylinositol phosphate kinase** is enhanced by nonreceptor tyrosine kinase)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2002:844588 CAPLUS
DOCUMENT NUMBER: 138:268816
TITLE: Type Iγ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions**
AUTHOR(S): Ling, Kun; Doughman, Renee L.; Firestone, Ari J.; Bunce, Matthew W.; Anderson, Richard A.
CORPORATE SOURCE: Department of Pharmacology, Program in Molecular and Cellular Pharmacology, University of Wisconsin Medical School, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Nature (London, United Kingdom) (2002), 420(6911), 89-93
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 07 Nov 2002
AB The ability of cells to form cell contacts, adhere to the extracellular matrix, change morphol., and migrate is essential for development, wound healing, metastasis, cell survival and the immune response. These events depend on the binding of integrin to the extracellular matrix, and assembly of focal **adhesions**, which are complexes comprising scaffolding and signalling proteins organized by **adhesion** to the extracellular matrix. Phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) regulates interactions between these proteins, including the interaction of vinculin with actin and talin. The binding of talin to β-integrin is strengthened by PtdIns(4,5)P2, suggesting that the basis of focal **adhesion** assembly is regulated by this lipid mediator. Here we show that the type I phosphatidylinositol phosphate kinase isoform-γ 661 (**PIPKI.gamma**.661), an enzyme that makes PtdIns(4,5)P2, is targeted to focal **adhesions** by an association with talin. **PIPKI.gamma**.661 is tyrosine phosphorylated by focal **adhesion** associated kinase signalling, increasing both the activity of phosphatidylinositol phosphate kinase and its association with talin. This defines a mechanism for spatial generation of PtdIns(4,5)P2 at focal **adhesions**.
CC 13-2 (Mammalian Biochemistry)
ST phosphatidylinositol phosphate kinase type I talin focal **adhesion**

IT Cell junction
(focal contact; type Iγ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)
IT Molecular association
(type Iγ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)
IT Phosphatidylinositol 4,5-bisphosphate
Talin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type Iγ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)
IT 104645-76-3, Phosphatidylinositol 4-phosphate 5-kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type Iγ phosphatidylinositol phosphate kinase targets and regulates focal **adhesions** through association with talin)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:430584 CAPLUS
DOCUMENT NUMBER: 143:4780
TITLE: The LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through an interaction with and activation of PIPKIα
AUTHOR(S): Kisseleva, Marina; Feng, Yungfeng; Ward, Michael; Song, Chunhua; Anderson, Richard A.; Longmore, Gregory D.
CORPORATE SOURCE: Departments of Medicine and Cell Biology, Washington University, St. Louis, MO, USA
SOURCE: Molecular and Cellular Biology (2005), 25(10), 3956-3966
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 20 May 2005
AB The phosphoinositide phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2] regulates the activity of many actin-binding proteins and as such is an important **modulator** of cytoskeleton organization during **cell migration**, for example. In **migrating cells** actin remodeling is tightly regulated and localized; therefore, how the PI(4,5)P2 level is spatially and temporally regulated is crucial to understanding how it controls **cell migration**. Here we show that the LIM protein Ajuba contributes to the cellular regulation of PI(4,5)P2 levels by interacting with and activating the enzymic activity of the PI(4)P 5-kinase (PIPKIα), the predominant enzyme in the synthesis of PI(4,5)P2, in a migration stimulus-regulated manner. In migrating primary mouse embryonic fibroblasts (MEFs) from Ajuba-/- mice the level of PI(4,5)P2 was decreased with a corresponding increase in the level of the substrate PI(4)P. Reintroduction of Ajuba into these cells normalized PI(4,5)P2 levels. Localization of PI(4,5)P2 synthesis and PIPKIα in the leading lamellipodia and membrane ruffles, resp., of migrating Ajuba-/- MEFs was impaired. In vitro, Ajuba dramatically activated the enzymic activity of PIPKIα while inhibiting the activity of PIPKIIβ. Thus, in addition to its effects upon Rac activity Ajuba can also influence **cell migration** through regulation of PI(4,5)P2 synthesis through direct activation of PIPKIα enzyme activity.

CC 13-6 (Mammalian Biochemistry)
ST Ajuba PIPKI assocn phosphatidylinositol bisphosphate formation **cell migration**; **phosphatidylinositol phosphate kinase** Ajuba **cell migration**
IT Molecular association
(Ajuba with PIPKIα and PIPKIIβ; LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LIM domain-containing, Ajuba; LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
IT **Cell migration**
Human
(LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
IT Phosphatidylinositol 4,5-bisphosphate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
IT Cell membrane
(PIPKIα in; LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
IT Organelle
(lamellipodium, PI(4,5)P2 in; LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
IT 104645-76-3, Phosphatidylinositol-4-phosphate 5-kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Iα and IIβ; LIM protein Ajuba regulates phosphatidylinositol 4,5-bisphosphate levels in **migrating cells** through interaction with and activation of PIPKIα)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1873 CAPLUS
DOCUMENT NUMBER: 142:89354
TITLE: Methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases
INVENTOR(S): Anderson, Richard A.; Ling, Kun; Doughman, Renee L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 47 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004265295	A1	20041230	US 2003-606038	20030625

PRIORITY APPLN. INFO.: US 2003-606038 20030625
ED Entered STN: 31 Dec 2004

AB The present invention relates to methods of identifying agents that **modulates** the activity of type I **phosphatidylinositol phosphate kinase** isoform .gamma.**661** (**PIPKI**.gamma.**661**) and methods of using such agents to prevent or treat a **cell migration**-mediated condition or disease in a subject are also provided. Specifically, the method involves contacting **PIPKI**.gamma.**661** with a test agent in the presence of at least one selected protein and detecting the activity of **PIPKI**.gamma.**661**, a change in the activity of **PIPKI**.gamma.**661** as compared to a control is indicative of said agent **modulating** the activity of PIPKI661. In one preferred embodiment, the agent **modulates** the activity of **Src** or **FAK** thereby **modulating** the activity of **PIPKI**.gamma.**661**. The present invention also relates to a method for identifying an agent that **modulates** cell focal **adhesion** assembly.

IC ICM G01N033-53
ICS G01N033-567; A61K038-48

INCL 424094500; 435007200

CC 9-2 (Biochemical Methods)
Section cross-reference(s): 1

ST drug screening **modulation** activity PIPKI **cell migration** mediated disease; **phosphatidylinositol phosphate kinase modulation** drug screening

IT Disease, animal
(**cell migration** associated; methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT Cell junction
(focal contact, **modulation** of; methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT **Cell migration**
Drug screening
Molecular cloning
(methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p125FAK; methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 141349-89-5, **SRC** kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 59977-48-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type I, isoform .gamma.**661**; methods for identifying agents **modulating** activity of **PIPKI**.gamma.**661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 818384-78-0 818384-79-1 818384-80-4 818384-81-5 818384-82-6
818384-83-7 818384-84-8 818384-85-9 818384-86-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; methods for identifying agents

modulating activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 818384-69-9 818384-70-2 818384-71-3 818384-72-4 818384-73-5
818384-74-6 818384-75-7 818384-76-8 818384-77-9 818384-87-1
818384-88-2 818384-89-3 818384-90-6 818384-91-7 818384-92-8
RL: PRP (Properties)
(unclaimed protein sequence; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)

IT 208183-74-8 818377-04-7 818377-05-8 818377-06-9 818377-07-0
RL: PRP (Properties)
(unclaimed sequence; methods for identifying agents **modulating** activity of **PIPKI.gamma.661** for preventing or treating **cell-migration** mediated conditions or diseases)

L14 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:771070 CAPLUS
DOCUMENT NUMBER: 139:347262
TITLE: The C-terminal Domain of Rac1 Contains Two Motifs That Control Targeting and Signaling Specificity
AUTHOR(S): van Hennik, Paula B.; ten Klooster, Jean Paul; Halstead, Jon R.; Voermans, Carlijn; Anthony, Eloise C.; Divecha, Nullin; Hordijk, Peter L.
CORPORATE SOURCE: Academic Medical Center, Sanquin Research at CLB and Landsteiner Laboratory, University of Amsterdam, Amsterdam, 1066 CX, Neth.
SOURCE: Journal of Biological Chemistry (2003), 278(40), 39166-39175
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Oct 2003
AB Rho-like GTPases control a wide range of cellular functions such as integrin- and cadherin-mediated **adhesion**, cell motility, and gene expression. The hypervariable C-terminal domain of these GTPases has been implicated in membrane association and effector binding. We found that cell-permeable peptides, encoding the C termini of Rac1, Rac2, RhoA, and Cdc42, interfere with GTPase signaling in a specific fashion in a variety of cellular models. Pull-down assays showed that the C terminus of Rac1 does not associate to either RhoGDI or to Pak. In contrast, the C terminus of Rac1 (but not Rac2 or Cdc42) binds to phosphatidylinositol 4,5-phosphate kinase (PIP5K) via amino acids 185-187 (RKR). Moreover, Rac1 assocs. to the adapter protein Crk via the N-terminal **Src** homol. 3 (SH3) domain of Crk and the proline-rich stretch in the Rac1 C terminus. These differential interactions mediate Rac1 localization, as well as Rac1 signaling, toward membrane ruffling, **cell-cell adhesion**, and **migration.** These data show that the C-terminal, hypervariable domain of Rac1 encodes two distinct binding motifs for signaling proteins and regulates intracellular targeting and differential signaling in a unique and non-redundant fashion.
CC 6-3 (General Biochemistry)
ST Rac1 protein motif signal transduction binding **phosphatidylinositol phosphate kinase**; Crk SH3 domain binding Rac1 **phosphatidylinositol phosphate**

kinase
IT **Adhesion**, biological
Signal transduction, biological
(C-terminal domain of Rac1 assocs. with effector and adapter proteins to regulate targeting and signaling specificity)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 16 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004143283 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15037311
TITLE: Talin: an emerging focal point of **adhesion** dynamics.
AUTHOR: Nayal Anjana; Webb Donna J; Horwitz Alan F
CORPORATE SOURCE: Department of Cell Biology, UVa School of Medicine, 1300 Jefferson Park Ave, PO Box 800732, Charlottesville, VA 22908-0732, USA.
SOURCE: Current opinion in cell biology, (2004 Feb) 16 (1) 94-8. Ref: 50
Journal code: 8913428. ISSN: 0955-0674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040324
Last Updated on STN: 20041015
Entered Medline: 20041014
AB The **adhesion** protein talin and the phosphoinositide PIP2 are emerging as key **modulators** of **adhesion** dynamics. Recent genetic studies on talin demonstrate its physiological role in organizing **adhesions**, stabilizing integrin-actin linkages and mediating integrin signaling in vivo. Biophysical force measurements provide further evidence that it is required for the reinforcement of the extracellular matrix-integrin-actin connection. Knockdown data along with structural analyses establish a major role for talin in 'inside-out' integrin activation through its direct interaction with integrin cytoplasmic domains. A recently uncovered role for talin is the recruitment of a **PIPKI gamma** isoform to **adhesions.** This introduces a novel connection between talin and PIP2 generation. Finally, PIP2 also stimulates the transient, direct binding interaction of the Arp2/3 complex with vinculin and thus may couple **adhesion** to actin assembly.
CT Animals
***Cell Adhesion**
***Cell Adhesion Molecules: ME, metabolism**
Cell Movement
Integrins: ME, metabolism
Phosphatidylinositol 4,5-Diphosphate: BI, biosynthesis
*Talin: PH, physiology

L14 ANSWER 10 OF 16 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004300117 EMBASE
TITLE: Competition for talin results in trans-dominant inhibition

of integrin activation.

AUTHOR: Calderwood D.A.; Tai V.; Di Paolo G.; De Camilli P.; Ginsberg M.H.
CORPORATE SOURCE: D.A. Calderwood, Department of Cell Biology, Scripps Research Institute, San Diego, CA 92037, United States. david.calderwood@ale.edu

SOURCE: Journal of Biological Chemistry, (9 Jul 2004) Vol. 279, No. 28, pp. 28889-28895.
Refs: 65
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040805
Last Updated on STN: 20040805

AB The ability of integrin **adhesion** receptors to undergo rapid changes in affinity for their extracellular ligands (integrin activation) is essential for the development and function of multicellular animals and is dependent on interactions between the integrin β subunit-cytoplasmic tail and the cytoskeletal protein talin. Cross-talk among different integrins and between integrins and other receptors impacts many cellular processes including **adhesion**, spreading, migration, clot retraction, proliferation, and differentiation. One form of integrin cross-talk, transdominant inhibition of integrin activation, occurs when ligand binding to one integrin inhibits the activation of a second integrin. This may be relevant clinically in a number of settings such as during platelet **adhesion**, leukocyte trans-migration, and angiogenesis. Here we report that competition for talin underlies the trans-dominant inhibition of integrin activation. This conclusion is based on our observations that (i) β tails selectively defective in talin binding are unable to mediate trans-dominant inhibition, (ii) trans-dominant inhibition can be reversed by overexpression of integrin binding and activating fragments of talin, and (iii) expression of another non-integrin talin-binding protein, **phosphatidylinositol phosphate kinase** type Iγ-90, also inhibits integrin activation. Thus, the sequestration of talin by the suppressive species is both necessary and sufficient for trans-dominant inhibition of integrin activation.

CT Medical Descriptors:
*protein binding
*binding competition
*signal transduction
*transdominant integrin activation inhibition
receptor affinity
protein protein interaction
cell adhesion
cell spreading
cell migration
blood clot retraction
cell proliferation
cell differentiation
ligand binding
thrombocyte adhesion
leukocyte migration
angiogenesis
gene overexpression
nonhuman
animal cell

article
nucleotide sequence
priority journal
Drug Descriptors:
*talin
*integrin
integrin receptor
ligand
protein subunit
cytoskeleton protein
peptide fragment
binding protein
talin binding protein
phosphatidylinositol 4 phosphate kinase
phosphatidylinositol 4 phosphate kinase type Igamma 90
unclassified drug

L14 ANSWER 11 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:396518 BIOSIS
DOCUMENT NUMBER: PREV200510186550
TITLE: Focal **adhesion** targeting of PIPKIgamma661 requires tyrosine phosphorylation of by **Src** and regulates an integrin-talin switch.
AUTHOR(S): Ling, Kun [Reprint Author]; Doughman, Renee L.; Firestone, Ari J.; Anderson, Richard
CORPORATE SOURCE: Univ Wisconsin, Dept Pharmacol, Madison, WI 53706 USA
SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp. C314.
Meeting Info.: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology. Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol Biol; Int Union Biochem & Mol Biol.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 2005
Last Updated on STN: 5 Oct 2005

AB Cell adherence to the extracellular matrix, is dependent on integrin assembly of focal **adhesions.** Phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P,) regulates interactions between these proteins, including the interaction of vinculin with actin and talin. The binding of talin to beta-integrin is strengthenedby PtdIns(4,5)P-2, suggesting that the basis of focal **adhesion** assembly is regulated by this lipid mediator. Here we show that the type I phosphatidylinositol phosphate kinase isoform-**gamma** 661 (**PIPKI gamma** 661), an enzyme that makes PtdIns(4,5)P,, is targeted to focal **adhesions** by an association with talin. **PIPKI gamma** 661 is tyrosine phosphorylated by focal **adhesion** associated kinase signalling, increasing both the activity of phosphatidylinositol phosphate kinase and its association with talin. The tyrosine phosphorylation of **PIPKI gamma** 661 on tyrosine 644 (Y644) is critical for its interaction with talin, and consequently, localization to FAs. **PIPKI gamma** 66I is specifically phosphorylated on Y644 by **Src** and this phosphorylation is regulated by focal **adhesion** kinase, which enhances an association between **PIPKI gamma** 661 and **Src.** The phosphorylation of Y644 results in a 15-fold increase in

binding affinity to the talin head domain and competes with integrin binding to talin. This defines a novel phosphotyrosine-binding site on the talin F3 domain and a "molecular switch" for talin binding between **PIPKI gamma** 66I and P-integrin that may regulate dynamic FA turnover. Supported by the NIH.

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Cell Biology

IT Chemicals & Biochemicals
focal **adhesion** kinase [EC 2.7.1.112]; **Src**; tyrosine; phosphatidylinositol-4,5-bisphosphate; beta-integrin; integrin; talin; focal **adhesion** protein; phosphatidylinositol phosphate kinase; type I phosphatidylinositol phosphate kinase isoform-gamma-661 [PIPKIgamma661]

L14 ANSWER 12 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:396265 BIOSIS
DOCUMENT NUMBER: PREV200510186297
TITLE: Type I gamma phosphatidylinositol phosphate kinase directly interacts with and is a substrate for Shp-1 tyrosine phosphatase.
AUTHOR(S): Bairstow, Shawn [Reprint Author]; Ling, Kun; Anderson, Richard
CORPORATE SOURCE: Univ Wisconsin, Dept Biomol Chem, Madison, WI 53706 USA
SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp. C259.
Meeting Info.: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology. Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol Biol; Int Union Biochem & Mol Biol.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 2005
Last Updated on STN: 5 Oct 2005

AB Tyrosine phosphorylation plays a critical role in several regulatory aspects of cellular signaling. Dephosphorylation of these residues is crucial for termination of signals initiated by tyrosine kinases. Previous work in our laboratory has shown that the tyrosine kinase **Src** phosphorylates Y644 on type I **gamma** phosphatidylinositol phosphate kinase (**PIPKI gamma** 661) in a focal **adhesion** kinase (**FAK**) dependent manner. Phosphorylation of this residue is key for high affinity binding of **PIPKI gamma** 661 to the focal **adhesion** protein talin and fortargeting of **PIPKI gamma** 661 to focal **adhesions** at the plasma membrane. A yeast 2-hybrid screen performed with the C-terminal 178 amino acid tail of **PIPKI gamma** 661 identified an interaction with the phosphatase domain of the tyrosine phosphatase Shp-1. We have subsequently shown that Shp-1 directly interacts with **PIPKI gamma** 661. In addition, we have evidence demonstrating that phosphorylated **PIPKI gamma** 661 can serve as a substrate for Shp-1 via in vitro phosphatase assays. Shp-1 phosphatase assays have also indicated that phosphatidylinositol 4,5-bisphosphate may be an important regulator of Shp- I phosphatase activity. Finally, we have also examined the impact of Shp-1 mediated dephosphorylation on the association between **PIPKI gamma** 661 and talin and targeting of **PIPKI gamma** 661 to focal **adhesions.**

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology
IT Parts, Structures, & Systems of Organisms
plasma membrane
IT Chemicals & Biochemicals
focal **adhesion** kinase [EC 2.7.1.112]; talin; tyrosine kinase **Src**; type-I-gamma phosphatidylinositol phosphate kinase: phosphorylation; Shp-1 tyrosine phosphatase

L14 ANSWER 13 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:396267 BIOSIS
DOCUMENT NUMBER: PREV200510186299
TITLE: Tyrosine Phosphorylation of Type I gamma **phosphatidylinositol phosphate kinase** by **Src** regulates an integrin-talin switch.
AUTHOR(S): Ling, Kun [Reprint Author]; Doughman, R. L.; Iyer, V. V.; Firestone, A. J.; Bairstow, S. F.; Mosher, D. F.; Schaller, M. D.; Anderson, R. A.
CORPORATE SOURCE: Univ N Carolina, Dept Cell and Dev Biol, Chapel Hill, NC 27599 USA
SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp. C259-C260.
Meeting Info.: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology. Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol Biol; Int Union Biochem & Mol Biol.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 2005
Last Updated on STN: 5 Oct 2005

AB Engagement of integrin receptors with the extracellular matrix induces the formation of focal **adhesions** (FAs). Dynamic regulation of FAs is necessary for **cells** to polarize and **migrate.** Key interactions between FA scaffolding and signaling proteins are dependent upon tyrosine phosphorylation. However, the precise role of tyrosine phosphorylation in FA development and maturation is poorly defined. Here we show that phosphorylation of type I gamma **phosphatidylinositol phosphate kinase** (**PIPKI** gamma **661**) on tyrosine 644 (Y644) is critical for its interaction with talin and consequently localization to FAs. PIPKI gamma 661is specifically phosphorylated on Y644 by **Src.** Phosphorylation is regulated by **FAK** which enhances the association between **PIPKI** gamma **661** and **Src.** The phosphorylation of Y644 results in similar to 15-fold increase in binding affinityto the talin head domain and blocks beta-integrin binding to talin. This defines a novel phosphotyrosine binding site on the talin F3 domain and a 'molecular switch' for talin binding between **PIPKI** gamma **661** and beta-integrin that regulates the generation of PI4,5P(2)at FAs and may regulate dynamic FAturnover.

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology
IT Parts, Structures, & Systems of Organisms
extracellular matrix
IT Chemicals & Biochemicals
signaling proteins; **Src**; beta-integrin; integrin; integrin

receptors; **FAK**; talin; P14 protein; type-I-gamma-**phosphatidylinositol phosphate kinase**: phosphorylation; phosphotyrosine binding site

L14 ANSWER 14 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:395646 BIOSIS
DOCUMENT NUMBER: PREV200510185678
TITLE: Nuclear phosphatidylinositol-4,5 bisphosphate generation regulates the assembly of splicing factor speckles and splicing of pre-mRNA.
AUTHOR(S): Song, Chunhua [Reprint Author]; Gonzales, Michael L.; Anderson, Richard A.
CORPORATE SOURCE: Univ Wisconsin, Sch Med, Dept Pharmacol, Madison, WI 53706 USA
SOURCE: FASEB Journal, (MAY 14 2004) Vol. 18, No. 8, Suppl. S, pp. C124.
Meeting Info.: Annual Meeting of the American-Society-for-Biochemistry-and-Molecular-Biology/8th Congress of the International-Union-for-Biochemistry-and-Molecular-Biology. Boston, MA, USA. June 12 -16, 2004. Amer Soc BioChem & Mol Biol; Int Union Biochem & Mol Biol.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 2005
Last Updated on STN: 5 Oct 2005

AB In mammals, there are three Phosphatidylinositol-phosphate Kinase type I (PIPK1) isoforms: PIPKI alpha, **PIPKI** beta, and **PIPKI gamma.** These isoforms each localize to distinct intracellular compartments, suggesting they **modulate** different functions. We have shown that PIPKI alpha and Phosphatidylinositol-4,5 bisphospha.te (PI4,5P(2)) generation co-localize with splicing factors innuclear speckles. Nuclear speckles, also called splicing factor compartments,are "depots" which harbor splicing factors and are associated with sites for active gene transcription and processing. Splicing factors translocate from these "depots" to sites of active gene transcription by mechanisms that are not yet understood. Here we show that PIPKI alpha is the major enzyme responsible for the synthesis of PI4,5P(2) in the nucleus. Furthermore we show that this nuclear PI4,5P(2) is responsible for maintaining splicing factors in nuclear speckles by regulating their phosphorylation. Finally we show that changes in splicing factor phosphorylation caused by **modulating** nuclear PI4,5P(2) levels can affect pre-mRNA splicing. Combined, these resultsdemonstrate that PIPKI alpha and PI4,5P(2) play a critical role in maintenance of splicing machinery organization and regulation of alternative pre-mRNA splicing.

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Cell Biology
IT Parts, Structures, & Systems of Organisms
nucleus
IT Chemicals & Biochemicals
splicing factor; phosphatidylinositol-4,5-biphosphate; pre-messenger RNA [pre-mRNA]; phosphatidylinositol-phosphate kinase type I isoform; phosphatidylinositol-phosphate kinase type I-alpha [PIPKI-alpha]; phosphatidylinositol-phosphate kinase type I-beta [PIPKI-beta]; phosphatidylinositol-phosphate kinase type I-**gamma** [**PIPKI-gamma**]; gene: transcription, processing

L14 ANSWER 15 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on

STN
ACCESSION NUMBER: 2003:149603 BIOSIS
DOCUMENT NUMBER: PREV200300149603
TITLE: Cell **adhesion**: A FERM grasp of membrane dynamics.
AUTHOR(S): Liddington, Robert C. [Reprint Author]; Bankston, Laurie A. [Reprint Author]; de Pereda, Jose M. [Reprint Author]
CORPORATE SOURCE: Program on Cell Adhesion, The Burnham Institute, 10901 North Torrey Pines Road, La Jolla, CA, 92037, USA rlidding@burnham.org
SOURCE: Current Biology, (February 4 2003) Vol. 13, No. 3, pp. R94-R95. print.
ISSN: 0960-9822 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Mar 2003
Last Updated on STN: 19 Mar 2003

AB Two recent papers provide the first evidence for a common mechanism of targeting and activation of an enzyme that is important in the rapid regulation of both focal **adhesion** assembly during **cell migration** and synaptic vesicle recycling at nerve terminals.

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Nervous System (Neural Coordination)

IT Parts, Structures, & Systems of Organisms
brain: nervous system; focal **adhesion**; membrane, dynamics; nerve terminal: nervous system; synaptic vesicle: nervous system

IT Chemicals & Biochemicals
focal **adhesion** kinase [EC 2.7.1.112]; integrin; integrin-beta; **phosphatidylinositol phosphate kinase** type 1-gamma; talin: FERM domain; vinculin

L14 ANSWER 16 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:391924 BIOSIS
DOCUMENT NUMBER: PREV200300391924
TITLE: Type Igamma phosphatidylinositol phosphate kinase targets to and regulates focal **adhesions.**
AUTHOR(S): Doughman, Renee L. [Reprint Author]; Ling, Kun; Firestone, Ari J.; Bunce, Matthew W.; Anderson, Richard A.
CORPORATE SOURCE: Pharmacology, University of Wisconsin-Madison, 1300 University Ave, Madison, WI, 53706, USA rldierckman@wisc.edu; kunling@wisc.edu; ajfirestone@wisc.edu; mwbunce@wisc.edu; raanders@wisc.edu
SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 628.1. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 2003
Last Updated on STN: 27 Aug 2003

AB The ability of cells to form cell contacts, adhere to the extracellular matrix, change morphology, and migrate are events essential for development, wound healing, metastasis, cell survival, and the immune response. These events are dependent upon integrin binding to the extracellular matrix and assembly of focal **adhesions.** Focal **adhesions** are complexes comprised of scaffolding and signaling

proteins organized by **adhesion** to the extracellular matrix. Phosphatidylinositol-4,5-bisphosphate (PI4,5P2) regulates interactions between these proteins, including the interaction of vinculin with actin and talin. The binding of talin to (-integrin is strengthened by PI4,5P2, suggesting that the basis of focal **adhesion** assembly is regulated by this lipid mediator. Here we show that the type I phosphatidylinositol phosphate kinase **gamma** (**PIPKI** (661), an enzyme that makes PI4,5P2, is targeted to focal **adhesions** by an association with talin. PIPKI(661 is tyrosine phosphorylated by focal **adhesion** associated kinase (**FAK**) signaling, increasing both PIP kinase activity and association with talin. This defines a mechanism for spatial generation of PI4,5P2 at focal **adhesions.**

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics)

IT Parts, Structures, & Systems of Organisms
extracellular matrix; focal **adhesions**

IT Chemicals & Biochemicals
actin; focal **adhesion** kinase [EC 2.7.1.112]: signaling; phosphatidylinositol-4,5-bisphosphate; talin; type 1 phosphatidylinositol phosphate-gamma; vinculin

=> □

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=> d que l25
L1            13 SEA (PIPKI OR PIPK) (3A) 661
L2           458 SEA PHOSPHATIDYLINOSITOL PHOSPHATE (2W) KINASE
L3            16 SEA L2 AND 661
L4            16 SEA L1 OR L3
L5        133994 SEA CELL (3A) MIGRAT?
L6             7 SEA L4 AND L5
L7            24 SEA L2 AND L5
L8            14 SEA L7 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L9            14 SEA L6 OR L8
L10            9 DUP REM L9 (5 DUPLICATES REMOVED)
L11           37 SEA (PIPKI OR PIPK) (3A) GAMMA
L12           23 SEA L11 AND (SRC OR FAK OR MODULAT? OR ADHESI?)
L13           18 SEA L12 NOT L10
L14           16 DUP REM L13 L10 (11 DUPLICATES REMOVED)
L15        25867 SEA ANDERSON R?/AU
L16          950 SEA LING K?/AU
L17           21 SEA DOUGHMAN R?/AU
L18        26801 SEA (L15 OR L16 OR L17)
L19           74 SEA L18 AND (L1 OR L2 OR L11)
L20           14 SEA L19 AND (L1 OR L11)
L21           74 SEA L18 AND L2
L22           26 SEA L21 AND (SRC OR FAK OR MODULAT? OR ADHES?)
L23           26 SEA L20 OR L22
L24           13 DUP REM L23 (13 DUPLICATES REMOVED)
L25            3 SEA L24 NOT L14


=> d ibib ca ct l25 1-3
'CA' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'
ENTER DISPLAY FORMAT (BIB):end

=> d ibib ab ct l25 1-3

L25  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:709891  CAPLUS
DOCUMENT NUMBER:          139:392716
TITLE:                    Phosphatidylinositol phosphate
                          kinases put PI4,5P2 in its place
AUTHOR(S):                Doughman, R. L.; Firestone, A. J.;
                          Anderson, R. A.
CORPORATE SOURCE:         Molecular and Cellular Pharmacology Program,
                          Department of Pharmacology, University of
                          Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE:                   Journal of Membrane Biology (2003), 194(2), 77-89
                          CODEN: JMBBBO; ISSN: 0022-2631
PUBLISHER:                Springer-Verlag New York Inc.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review. Phosphatidylinositol 4,5-bisphosphate (PI4,5P2) is a critical 2nd
     messenger that regulates a myriad of diverse cellular activities including
     modulation of the actin cytoskeleton, vesicle trafficking, focal
     adhesion formation, and nuclear events. In order to effectively
     regulate these disparate cellular events, the biosynthesis of PI4,5P2 by
     phosphatidylinositol phosphate kinases (PIP
     kinases) must be both spatially and temporally regulated. Two
     subfamilies of PIP kinases, types I and II, allow the generation of
     PI4,5P2 from independent pools of substrate, PI(4)P and PI(5)P resp. In
     turn, type I and II PIP kinases show different subcellular localization
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and thus are involved in distinct signaling pathways. Addnl., several type I isoforms, and their splice variants, have now been shown to be differentially localized throughout the cell and to be involved in the synthesis of PI4,5P2 at distinct sites. These findings implicate PIP kinases as the major regulators of PI4,5P2-mediated events, making them key signaling enzymes in a variety of processes. Understanding the mechanisms regulating spatial and temporal biosynthesis of PI4,5P2 by PIP kinases is vital for understanding these processes as a whole. This review examines both structural and regulatory features that **modulate** activity, localization, and substrate usage of PIPKs.

CT Signal transduction, biological

CT Phosphatidylinositol 4,5-bisphosphate

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:862702 CAPLUS

DOCUMENT NUMBER: 138:302408

TITLE: Inhibition of Phosphatidylinositol-4-phosphate 5-Kinase Ialpha Impairs Localized Actin Remodeling and Suppresses Phagocytosis

AUTHOR(S): Coppolino, Marc G.; Dierckman, Renee; Loijens, Joost; Collins, Richard F.; Pouladi, Mahmoud; Jongstra-Bilen, Jenny; Schreiber, Alan D.; Trimble, William S.; **Anderson, Richard**; Grinstein, Sergio

CORPORATE SOURCE: Department of Biochemistry, University of Toronto, Hospital for Sick Children, Cell Biology Program, ON, M5G 1X8, Can.

SOURCE: Journal of Biological Chemistry (2002), 277(46), 43849-43857
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Actin polymerization drives the extension of pseudopods required for phagocytosis. Phosphatidylinositol 4,5-bisphosphate (PIP2) is thought to play a central role in this process, because it interacts with several actin-regulatory proteins and undergoes acute and localized changes at sites of phagocytosis. The authors therefore studied whether phosphatidylinositol-4-phosphate 5-kinase (PIPK), the enzyme responsible for the generation of PIP2 from phosphatidylinositol 4-phosphate, is involved in the control of phagocytosis. PIPKIα was found to accumulate transiently on forming phagosomes. To test the functional involvement of PIPKIα in particle engulfment, the authors generated a double mutant (D309N/R427Q) that lacks kinase activity. When ectopically expressed in cultured cells, this mutant is targeted to the plasma membrane and accumulates at the phagosomal cup during particle engulfment. Expression of PIP5KIα D309N/R427Q impaired phagocytosis in RAW264.7 macrophages and in engineered phagocytes generated by transfection of Fc receptors in Chinese hamster ovary cells. Inhibition of phagocytosis could not be attributed to defects in particle binding or receptor clustering, which was monitored using green fluorescent protein-tagged Fcγ receptors. Instead, expression of the inactive kinase diminished the accumulation of PIP2 and of F-actin in the phagosomal cup. Thus, PIPKIα activity is involved in the actin remodeling that is a prerequisite for efficient phagocytosis. PIPKIα appears to contribute to the transient changes in PIP2 levels that are associated with, and likely required for, the recruitment and regulation of actin-**modulating** proteins.

CT Actins
CT Phagocytosis
CT Phosphatidylinositol 4,5-bisphosphate
CT Phosphatidylinositol 4-phosphate
CT Macrophage
CT Actins
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:607217 CAPLUS
DOCUMENT NUMBER: 113:207217
TITLE: The human erythrocyte contains two forms of phosphatidylinositol-4-phosphate 5-kinase which are differentially active toward membranes
AUTHOR(S): Bazenet, Chantal E.; Ruiz Ruano, Antonio; Brockman, Jennifer L.; **Anderson, Richard A.**
CORPORATE SOURCE: Med. Sch., Univ. Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of Biological Chemistry (1990), 265(29), 18012-22
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A human erythrocyte cytosolic phosphatidylinositol-4-phosphate 5-kinase (PIP kinase) and a membrane-bound PIP kinase have been purified by phosphocellulose chromatog. Fractionation of the membrane-bound PIP kinase activities by phosphocellulose separated activity into two peaks, which eluted at 0.6 M NaCl (type I PIP kinase) and 1.0M NaCl (type II PIP kinase). The cytosolic PIP kinase and the membrane-bound type II PIP kinase are 53 kDa by SDS-PAGE, have indistinguishable 125I-peptide maps, and are immunochem. indistinguishable, suggesting that they are sequence identical. Antibodies raised to the cytosolic PIP kinase inhibit activity of both the membrane-bound type II and the cytosolic PIP kinases. The type I PIP kinase appears to be distinct from the cytosolic and membrane-bound type II PIP kinase; it is not immunocross-reactive, and antibodies toward type II PIP kinases do not inhibit type I PIP kinase. Further, membrane-bound type II PIP kinase can be removed from type I PIP kinase without loss of activity. Functional characterization of the PIP kinases demonstrates that the type I kinase has a 10-fold lower Km for PIP and a 5-fold higher Km for ATP compared with the type II enzymes. The type I and type II (membrane-bound or cytosolic) PIP kinases are **modulated** differentially by spermine and heparin. Finally, the type I PIP kinase phosphorylates intrinsic PIP on isolated erythrocyte membranes, whereas the type II PIP kinases have no activity toward native membranes.
CT Michaelis constant
CT Erythrocyte
CT Membrane, biological
CT Cytoplasm
CT Phosphoinositides

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